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# Introduction to the Health Effects Institute Environmental Epidemiology Planning Project Documents

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In recent years, the attention of the scientific community and of the public at large has focused more on environmental causes of human disease. In response, many branches of science have contributed to the study of the health effects of environmental pollutants. Epidemiology, the study of the distribution and determinants of human disease, has played a unique and critical role in this effort. Data from well-designed and carefully executed epidemiologic studies can measure the effects of pollutant exposures under the conditions most relevant to human experience and therefore can be especially informative about the causes of human disease. For this reason, epidemiologic data can make a unique contribution to regulatory decisions.

However, epidemiologic research on the health effects of environmental pollutants has proven difficult to conduct. In epidemiologic studies, the amount of exposure sustained by study subjects and the conditions under which that exposure occurs generally are beyond the direct control of the investigator. Human populations are exposed to multiple pollutants whose individual, let alone joint, effects are not known. Under these conditions, inaccurate measurement of exposure and the effects of extraneous factors on disease occurrence often present major threats to study validity. Epidemiologic research strategies and methods for improving exposure assessment and for measuring health effects under such real world conditions are still in their infancy; their maturation could provide the basis for substantial gains in knowledge about environmental causes of human disease, which, in turn, could provide a more scientifically sound basis for public health policy.

In December 1989, the U.S. Environmental Protection Agency (EPA) asked the Health Effects Institute (HEI) to identify research needs and opportunities in environmental epidemiology. Founded in 1980, HEI is a non-profit research institute that funds research on the health effects of automotive emissions with funds provided in equal amounts by the EPA and the automotive industry. HEI operates according to a mechanism designed to assure autonomy in the setting of research priorities and the disbursement of funds.

In response to the EPA's request, HEI conducted an environmental epidemiology planning project that brought together epidemiologists and other health and environmental scientists to address four selected areas of epidemiologic research. Three of these areas, electric and magnetic fields, indoor air pollution and other complex mixtures, and tropospheric ozone, involve environmental exposures of current scientific and regulatory interest. The fourth, methodologic issues, explores issues in the design and conduct of research that have implications for the study of health effects of many environmental agents.

The four general objectives of the planning project were *a*) to characterize the state of, and to identify gaps in, current knowledge in selected areas of environmental epidemiology and methodologic issues relevant to the design, conduct, analysis, and interpretation of environmental epidemiologic studies; *b*) to identify research needs and opportunities in the selected areas of environmental epidemiology; *c*) to communicate the results of the planning effort to the scientific and regulatory communities and the general public; and *d*) to aid HEI in the development of its own research programs in these research areas.

Working groups were assembled to address each of the four areas of research

and were asked to produce working papers (Appendix A). Drafts of working papers were discussed at workshops held during the spring and summer of 1991, and revisions were made based upon these discussions. Revised papers were reviewed by two external reviewers and an internal HEI reviewer (Appendix B). The results of these efforts are contained in the four sets of collected papers that are published in this issue.

The project was designed to afford key researchers the opportunity to address important problems in environmental epidemiology while exploring new avenues for epidemiologic research. HEI did not ask the working groups to arrive at a consensus about their areas of research but rather, to quote University of North Carolina at Chapel Hill epidemiologist David Savitz, "to focus on the frontiers of existing knowledge and make recommendations about how to extend those frontiers" (1).

Hence, the papers do not necessarily reflect the views of HEI or the project's sponsors, which was intended. Neither was it our goal to achieve a uniformity of style or presentation; rather, we encouraged the working groups to define independently both the specific issues they would address and the manner in which they would address them. The resulting documents are a collection of papers that reflect each author's views as they emerged from collective discussion with members of their working group and the review process described above.

Each collection of papers offers thoughtful overviews, insightful critiques of current practice, and useful recommendations. The Working Group leaders have summarized the main conclusions and recommendations offered by their working groups in separate chapters of each document (1–5).

Several papers in the "Methodologic Issues" document address the critical problem

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of measurement error in the characterization of exposure and argues for a reexamination of the potential contribution of ecologic or aggregate level studies in environmental epidemiology. Hatch and Thomas (6) critically discuss a variety of methods available to the epidemiologist to characterize environmental exposure and dose including pharmacokinetic and other models based on explicit biologic theories, sensitivity analyses, and study designs for increasing the precision of exposure measurement. Prentice and Thomas (7) review the statistical approaches available to account for measurement error. The articles by Morgenstern and Thomas (8) and Prentice and Thomas (7) argue for increased efforts in methods research on the theory, design, and conduct of aggregate level studies for understanding and reducing the acknowledged biases that impede the use of a potentially informative and efficient approach. Greenland (9) reviews the theoretical and practical issues that make the epidemiologic measurement of the effect of multiple exposures so difficult and concludes that a focus on the effects of the exposure mixture, rather than on the separate effects of its constituents, may be all that can be accomplished in most circumstances.

The current scientific interest in the health effects of electric and magnetic fields stems mostly from epidemiologic observations of increased rates of leukemias and central nervous system cancers among children exposed in the home and among certain occupational groups. The "Electric and Magnetic Fields" document offers comprehensive and critical reviews of existing knowledge about electric and magnetic fields (EMF) health effects in two areas that have, until now, received limited attention: adverse reproductive outcomes (10) and neurobehavioral effects (11). In addition, Kaune provides a comprehensive background discussion of the technical aspects of the measurement of fields (12) and then addresses the critical area of exposure characterization and measurement (13) in the context of epidemiologic research.

The collected papers in the "Indoor Air and Other Complex Mixtures" document considers the daunting task of epidemiologically studying the effects of simultaneous exposure to multiple pollutants. An important point addressed at length by Leaderer, et al. (14) is that improving the quality of exposure measurement would increase the informativeness of studies of multiple exposures. This echoes the views of Hatch and Thomas (6) and is emphasized by Greenland (9).

The health effects of tropospheric (ground level) ozone have been and remain an area of

intense research activity for HEI and other organizations. Nevertheless, it is an area in which epidemiologic research on its long-term exposure effects is lacking and desperately needed. The collected papers in the "Tropospheric Ozone" document offers a perspective on future epidemiologic research, expounded in particular by Tager (4), that focuses on understanding the pathophysiologic processes and subclinical abnormalities that may constitute a relation between exposure and chronic disease. Balmes (15) critically reexamines the evidence, often viewed as conflicting, in search of a relation between the exacerbation of asthma (e.g., increased attack rates) and exposure to ozone, and he argues for more research on this subject.

It is noteworthy that because the planning project documents are diverse by design common threads run through them. As noted above, all four documents emphasize the need for methodologic advances in the measurement and characterization of environmental exposures for epidemiologic research. This common emphasis should not be surprising to epidemiologists, who have acknowledged that for a long time exposure assessment is the critical weakness in environmental epidemiology. Another recurring theme is the need to integrate observational epidemiologic research with experimental biologic and clinical research. In "Indoor Air and Other Complex Mixtures," Mauderly addresses the respective roles of toxicologic and epidemiologic research (16), Wilcosky examines the use of laboratory-derived markers of early disease (17), and McDonnell examines the incorporation of controlled human exposure studies into epidemiologic research protocols (18). The theme of integration of knowledge from experimental biology and epidemiology appears again in "Electric and Magnetic Fields," in which Stevens (19) proposes biologically based epidemiologic research on the carcinogenicity of electric and magnetic fields and in "Tropospheric Ozone," in which Devlin (20) discusses possible approaches to the development of biologic markers of exposure to ozone and early effects of this exposure. Balmes (15) proposes the incorporation of controlled human exposure experiments within observational study designs. In "Methodologic Issues," Hatch and Thomas (6) stress the need for the development of epidemiologically useful biologic markers of exposure and call the attention of biologists and epidemiologists to the necessary characteristics of such markers and potential pitfalls in their use.

The planning project was a cooperative venture between HEI and members of the

environmental epidemiology research community. Project oversight was provided by a steering committee that included members of the HEI Research and Review Committees (Appendix C), several of whom served as observers and liaisons between the working groups and HEI staff. The EPA and a diverse group of private sector organizations (Appendix D) provided financial support for the project. Scientists recommended by the sponsoring organizations served as observers and liaisons between the sponsors and the working groups (Appendix A) and offered advice and commentary throughout the project.

The planning project documents already have made a valuable contribution to research planning at HEI. We hope that others will find them thought-provoking and useful for planning environmental health research. ♣

## Appendices

### Appendix A: Working Group Members, HEI Environmental Epidemiology Planning Project

*Authors of the Working Group on Methodologic Issues.* Kenneth J. Rothman, Working Group leader, editor, *Epidemiology*; Maureen O. Hatch, Columbia University School of Public Health; Hal Morgenstern, UCLA School of Public Health; Raymond Neutra, California Department of Health Services; Ross L. Prentice, Fred Hutchinson Cancer Research Center; Duncan Thomas, University of Southern California; and Dimitrios Trichopoulos, Harvard School of Public Health.

*HEI Steering Committee Liaisons of the Working Group on Methodologic Issues.* Richard Remington, University of Iowa and John Tukey, Princeton University.

*Sponsor Observers and Liaisons of the Working Group on Methodologic Issues.* John F. Aquavella, Monsanto Company and Gerhard K. Raabe, Mobil Oil Corporation.

*Authors of the Working Group on Electric and Magnetic Fields.* David A. Savitz, Working Group leader, University of North Carolina at Chapel Hill; William T. Kaune, EM Factors; Nigel Paneth, Michigan State University; Gary Shaw, March of Dimes, California Birth Defects Monitoring Program; Jack Siemiatycki, Institut Armand-Frappier; and Richard Stevens, Battelle Pacific Northwest Laboratories.

*HEI Steering Committee Liaison of the Working Group on Electric and Magnetic Fields.* Arthur Upton, New York University.

*Sponsor Observers and Liaisons of the Working Group on Electric and Magnetic Fields.* Donald A. Greschaw, Ford Motor Company and an alternate, Rebecca Calderon, U.S. Environmental Protection Agency.

**Authors of the Working Group on Indoor Air and Other Complex Mixtures.**

Jonathan M. Samet, Working Group leader, University of New Mexico Cancer Center; Frank Speizer, Working Group leader, Harvard Medical School; Douglas Dockery, Harvard School of Public Health; Sander Greenland, UCLA School of Public Health; Brian Leaderer, Yale University; Paul Lioy, UMDNJ-Robert Wood Johnson Medical School; Joe Mauderly, Inhalation Toxicology Research Institute; William F. McDonnell, U.S. Environmental Protection Agency; Carl Shy, University of North Carolina at Chapel Hill; John Spengler, Harvard School of Public Health; Noel Weiss, University of Washington; and Timothy Wilcosky, Research Triangle Institute.

**HEI Steering Committee Liaisons of the Working Group on Indoor Air and Other Complex Mixtures.** Leon Gordis, Johns Hopkins University; Curtis Harris, National Cancer Institute; and Mark Utell, University of Rochester Medical Center.

**Sponsor Observers and Liaisons of the Working Group on Indoor Air and Other Complex Mixtures.** Irwin H. Billick, Gas Research Institute; Robert S. Dyer, U.S. Environmental Protection Agency; and alternates Neil C. Hawkins, Dow Chemical Company and Ronald E. Wyzga, Electrical Power Research Institute.

**Authors of the Working Group on Tropospheric Ozone.** Ira Tager, Working Group leader, Veterans Administration Medical

Center; John Balmes, San Francisco General Hospital; David Bates, Vancouver, British Columbia, Canada; Robert Devlin, U.S. Environmental Protection Agency; Morton Lippmann, New York University; Alvaro Muñoz, Johns Hopkins School of Hygiene and Public Health; and Bart D. Ostro, California Department of Health Services.

**HEI Steering Committee Liaison of the Working Group on Tropospheric Ozone.** Millicent Higgins, National Heart, Lung and Blood Institute.

**Sponsor Observers and Liaisons of the Working Group on Tropospheric Ozone.** Jaroslav J. Vostal, General Motors Corporation and Barbara Divine, Texaco, Inc.

## Appendix B: Reviewers

**Methodologic Issues.** John Bailar, McGill University; Lewis Kuller, University of Pittsburgh School of Public Health; and James H. Ware, Harvard School of Public Health.

**Electric and Magnetic Fields.** Gareth Green, Harvard School of Public Health; Charles Poole, Boston University School of Public Health; and Roy Shore, New York University Medical Center, Institute of Environmental Medicine.

**Indoor Air and Other Complex Mixtures.** Nathaniel Cobb, Centers for Disease Control-CEHIC; Ruth Etzel, Centers for Disease Control-CEHIC; Henry Falk, Centers for Disease Control-CEHIC; William E. Fayerweather, DuPont Company; Bernard Goldstein, Environmental and Community

Medicine, UMDNJ, Robert Wood Johnson Medical School; David Mannino, Centers for Disease Control; and Roger McClellan, Chemical Industry Institute of Toxicology.

**Tropospheric Ozone.** Joseph D. Brain, Harvard School of Public Health; Patricia Buffler, University of California at Berkeley; and Roger Detels, UCLA School of Public Health.

## Appendix C: Project Oversight

**HEI Steering Committee.** Leon Gordis, chairman, Johns Hopkins University, School of Public Health; Curtis Harris, National Cancer Institute; Millicent Higgins, National Heart, Lung and Blood Institute; Richard Remington, University of Iowa; John Tukey, Princeton University; Arthur Upton, New York University; and Mark Utell, University of Rochester Medical Center.

**HEI Staff.** Aaron J. Cohen, staff scientist; Noreen S. Manzo, administrative coordinator; Kathleen M. Nauss, director for scientific review and evaluation; Andrew Sivak, recent president (1989–1992); and Jane Warren, director of research.

## Appendix D: Project Sponsors

The U.S. Environmental Protection Agency, The American Petroleum Institute, The Engine Manufacturers Association, The Motor Vehicles Manufacturers Association, The Chemical Manufacturers Association, The Electrical Power Research Institute, and The Gas Research Institute.

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